REMARKS

Upon entry of this amendment, claims 1, 7-13, and 21-31 are currently pending in the instant application. Claims 21-29 have been withdrawn. Claim 1 has been amended. Support for the subject matter of claim 1 can be found throughout the specification, *inter alia,* page 4, paragraph 2. New claims 30 and 31 have been added. Support for the subject matter of new claim 30 can be found throughout the specification, *inter alia,* Example 4.3, page 34. Support for the subject matter of new claim 31 can be found throughout the specification, *inter alia,* page 12, last paragraph, spanning the top of page 13 and page 17, paragraph 4.

No new matter has been added. In light of the above amendments, claims 1, 7-13, 30 and 31 are under active consideration in this application.

Objections to the Disclosure

The disclosure is objected to for an informality at page 5, line 7 which reads "1985-1902". The specification has been amended to correct this minor typographical error. The corrected page numbers now read "1895-1902". No new matter has been added.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 1, 3, 4, 7, and 8 are rejected under 35 U.S.C. §112, second paragraph as being indefinite.

According to the Examiner, claim 1 (and claims 7 and 8 dependent thereon) is unclear as to whether or not the method is performed with a test system that includes a hyperactivated macrophage.

In response, Applicants submit that claim 1, as amended, recites a method for determining whether a substance is an activator or an inhibitor of an inflammatory process...wherein the inhibitor of ARL4 is a substance which inhibits the inflammatory process. The inflammatory process recited in claim 1 (and claims 7 and 8 dependent thereon) is one "in which a macrophage is in a hyperactivated status due to up-regulated ARL4". The test system, itself, however, does not require the presence of a

hyperactivated macrophage. Such cellular and cell-free test systems are known by one skilled in the art and are described in the specification. Applicants direct the Examiner's attention to pages 12-13 wherein such systems are generally described:

> A test system of the invention comprises, for example, elements well known in the art. For example, cell-free systems may include but are not limited to, a said protein or a functional equivalent, derivative, variant, mutant or fragment of a said protein of the invention, a nucleic acid encoding a said protein or encoding a functional equivalent, derivative, variant, mutant or fragment of a said protein of the invention in soluble or bound form or in cellular compartments or vesicles. Suitable cellular systems include, for example, a suitable prokaryotic cell or eukaryotic cell, *e.g.* such cell comprising a said protein of the invention or a functional equivalent, derivative, variant, mutant or fragment of a said protein of the invention, a nucleic acid encoding a said protein or encoding a functional equivalent, derivative, variant, mutant or fragment of a said protein of the invention (Tsuchiya, S. *et al.* (1980) Int. J. Cancer 26, 171-176; Ziegler-Heitbrock, H.W. *et al.* (1988) Int. J. Cancer 41, 456-461). A cell suitable for use in a said test system of the invention may be obtained by recombinant techniques, *e.g.* after transformation or transfection with a recombinant vector suitable for expression of a desired protein of the invention or functional equivalent, derivative, variant, mutant or fragment of a said protein of the invention, or may *e.g.* be a cell line or a cell isolated from a natural source expressing a desired protein of the invention or functional equivalent, derivative, variant, mutant or fragment of a said protein. A test system of the invention may include a natural or artificial ligand of the protein selected from the group consisting of: MIF, DAD1, ARL4, GNS, Transglutaminase 2, Stearyl-CoA-Desaturase and UDP-Glucose Ceramide Glycosyltransferase if desirable or necessary for testing whether a substance of interest is an inhibitor or activator of a said protein of the invention.

Applicants further direct the Examiner's attention to Example 4.3, page 34 which describes a cell-free GTPγS binding assay. Applicants also direct the Examiner's attention to page 13, paragraph 1 which describes what is meant by measurable "read-out".

In light of the above remarks and amendments, Applicants submit that claim 1 (and claims 7 and 8 dependent thereon) is clearly defined. Thus, this rejection with respect to these claims is overcome.

According to the Examiner, claims 3 and 4 are unclear in the recitations of "directly" and "indirectly", respectively.

Claims 3 and 4 have been cancelled, thereby making this rejection moot with respect to these claims.

In light of the above amendment and remarks, it is submitted that all the rejections under Section 112, second paragraph have been obviated and must be withdrawn.

Section 102 Rejections

Claims 1, 4 and 7 are rejected under 35 U.S.C. §102(b) as being anticipated by Peterson *et al.* United States Patent No. 5,883,084 ("Peterson *et al.*").

Claims 1, 4, 7 and 8 are rejected under 35 U.S.C. §102(b) as being anticipated by Fuhrman *et al.* United States Patent No. 5,470,885 ("Fuhrman *et al.*").

As a preliminary matter, Applicants point out that claim 4 has been canceled thereby making these rejections moot with respect to this claim.

Applicants respectfully disagree with these rejections under Section 102(b) and, for the reasons detailed below, submit that the subject matter of claims 1, 7, and 8 is in no way anticipated by the cited references.

To constitute an anticipation, each and every element of the claim must be disclosed in that one reference. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1985). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed..." Structural *Rubber Prod. Co. v. Park Rubber Co.*, USPQ 1264 (Fed. Cir. 1984). Thus, to constitute an anticipation, a printed publication must describe the invention. The decided case law makes clear that the description must be adequate to a person with ordinary skill in the art to enable that person both to comprehend the invention, and also to make the invention without undue experimentation, without relying on his own inventive capabilities or on the teaching of the application. As detailed below, the cited reference neither describes nor enables the presently claimed subject matter.

The Present Claims

Claim 1, as now amended, is specifically drawn to a method for determining whether a substance is an activator or an inhibitor of *an inflammatory process in which a macrophage is in a hyperactivated status due to up-regulated ARL4* comprising: (a) applying the substance to a test system which generates a measurable read-out upon modulation of ARL4 or a biological function of ARL4; and (b) comparing the level of read-out of the test system to a control level, wherein a difference in levels indicates the substance is an inhibitor or an activator ofARL4; and wherein the inhibitor of ARL4 is a substance which inhibits the inflammatory process, and wherein the method is performed using a cellular system (claim 7).

Peterson *et al*

According to the Examiner, Peterson *et al.* teach it is of interest to reduce the inflammatory activity of alveolar macrophages in respiratory diseases such as COPD and use a test system which comprises cultured cells.

Novelty of the Present Claims

In complete contrast, as presently amended, claims 1 and 7 are specifically drawn to a method for determining whether a substance is an activator or an inhibitor of *an inflammatory process in which a macrophage is in a hyperactivated status due to up-regulated ARL4*. Applicants direct the Examiner's attention to the Examples 1.1, page 18 and Example 4, pages 31-32 which teaches that macrophages in particular inflammatory processes show particular gene expression patterns, *i.e.*, although cigarette smoking attracts macrophages involved in an inflammatory process, macrophages from "healthy" smokers (not suffering from COPD) show a different gene expression pattern than macrophages from smokers who have COPD, known as a "hyperactivated macrophage".

Person *et al.* deals with the inhibition of macrophage activation. In contrast, the present invention is directed to a method for finding inhibitors of an inflammatory process *in which a macrophage is in a hyperactivated status due to up-regulated ARL4* – this

means that activated macrophages are still present. The instant invention, therefore, is superior over Peterson *et al.* since Peterson *et al.* try to inhibit the inflammatory activity of macrophages, thus, the positive action an activated macrophage which is an essential part of a well-functioning immune system is blocked too and will harm the immune system. In the present invention, the pathogenic function of the hyperactivated macrophage is inhibited, however, the function of the activated macrophage is left alone. Since the target of the instant invention differs significantly from that of Peterson *et al.*, the cited reference does not anticipate claimed methods. Accordingly, this rejection based on Section 102(b) must be withdrawn.

Fuhrman *et al.*

According to the Examiner, Fuhrman *et al.* show a test system involving use of activated alveolar macrophages and a test compound (PFOB). The read-out is in terms of peroxide and free radical production. Macrophages are used at the first stage, while the read-out is performed on cell-free supernatants.

Novelty of the Present Claims

As discussed above, in complete contrast, as presently amended, claims 1 (and claims 7 and 8 dependent thereon) are specifically drawn to a method for determining whether a substance is an activator or an inhibitor of *an inflammatory process in which a macrophage is in a hyperactivated status due to up-regulated ARL4*... and wherein the inhibitor of ARL4 is a substance which inhibits the inflammatory process. Thus, the core of the present invention is that ARL4 must be inhibited to cure certain inflammatory processes, *e.g.*, COPD. The cited reference, therefore, does not anticipate claimed methods. Accordingly, this rejection based on Section 102(b) must be withdrawn.

Allowable Subject Matter

Applicants gratefully acknowledge the Examiner's finding that claims 9-13 are allowable over the prior art.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that all of the objections and rejections have been overcome and must be withdrawn. Further, Applicants submit that the application is now in form for issuance and an early allowance is earnestly requested. If any issues remain, the Examiner is invited to telephone the Attorney at the number below

Respectfully submitted,

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